IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
NICHOLAS S. BODOR	)	Art Unit: 125
Serial No. 807,034	)	Examiner: Elbert L. Roberts
Filed: December 9, 1985	)	
For: SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY	)	

89-2082

REPLY UNDER 37 C.F.R. §1.111

Honorable Commissioner of Patents and Trademarks
Washington, D. C. 20231

Sir:

In complete response to the Official Action mailed March 28, 1986, applicant respectfully requests reexamination and reconsideration of the application identified in caption, pursuant to 37 C.F.R. §1.112, and in light of the remarks which follow.

At the outset, as briefly discussed with the Examiner over the telephone, it is believed that the most pertinent prior art has not yet been made of record. It was agreed that this response would formally identify such prior art, as well as best distinguish applicant's invention thereover.

Thus, the prior art in question consists of U. S. Patents Nos. 4,242,334 and 4,377,575, both to Stache et al (copies attached). The '334 patent relates to certain corticoid 17-(alkyl carbonates) necessarily comprising, e.g., a reverse ester function, bonded strictly to a methylene

bridge depending from a 20-keto group. The '575 patent features related corticoid 17-(alkyl carbonates), but wherein the methylene moiety is a terminal group, not a bridge, and is necessarily halogenated.

More importantly, though, it is submitted that these anti-inflammatory "carbonate" patents themselves point to, rather than detract from, the non-obviousness and hence patentability of the instantly claimed compounds, and clearly establish that the prior art steroidal esters and carbonates are not equivalent. Especially note the "steroids" case of In re Grunwell and Petrow, 203 U.S.P.Q. 1055.

An overview of applicant's invention is first in order. Applicant's "soft drug" approach*/ is a marked departure from traditional drug design based on structure/activity relationships, and emphasizes the factor of safety over that of intrinsic activity. Indeed, the ways in which the toxic dose of a target compound may be reduced depend upon the alteration of the disposition of the drug in the body. Thus, through the prodrug approach, the compound may be modified so that it is inactive of itself, but once it reaches its site of action, it becomes activated and produces its therapeutic effect. Hence, the distribution of the target compound is modified to reduce its undesired interaction with sites of action other than where it is wanted. The toxicity of the target compound may be divided into its intrinsic toxicity, which is related to its intrinsic activity, and the toxicities of its metabolites

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*/ See pages 2 and 3, and the paragraph bridging pages 6 and 7, of applicant's specification.

which may be inactive, active, or reactive. The toxicity of the inactive metabolite is, of course, zero, but those of the others are not. The toxicity of the active metabolites is of the same order as the intrinsic toxicity of the drug itself, but the pharmacokinetic distribution is different and therefore uncontrollable. The toxicity of the reactive metabolites is of a different order, and is the most important to avoid. Reactive metabolites are known to combine with DNA and other critical cellular macromolecules to produce mutations, cancer, and cellular necrosis. Since reactive drug metabolites are products of a reaction with enzymatically produced active oxygen, the avoidance of this route of metabolism will reduce a large portion of the toxicity of the lead compound.

The present invention, geared to <u>specific</u> derivatives, e.g., of hydrocortisone, features derivatizing known endogenous inactive metabolites of, e.g., hydrocortisone, for example, 11β, 17α-dihydroxy-androst-4-ene-17β-carboxylic acid, or cortienic acid, with metabolically labile biofunctional <u>carbonate</u> moieties. Such modification as to form a soft drug, which would have the same order of potency but a much lower order of toxicity, is a marked departure from use of ester groups (see the prior art already of record) which have been shown to be effective in producing <u>highly</u> <u>active</u> compounds for dermal application (i.e., the antithesis of the "soft" drug approach).

Moreover, it too would have been expected by those skilled in this art that the simple 17β-esters would be subjected to intramolecular group transfer of the acyl moiety

to the 17β-position, forming a reactive mixed anhydride species. This is precisely the situation that the soft drug approach seeks to avoid. The likely candidates for reaction with this type of reactive intermediate, the plasma proteins, would then be made immunogenic and cause unwanted side effects in such manner. The systemic lupus which is seen in some cases of hypercortisolism is, in fact, attributed to just such a mechanism. The cortisol is postulated to react with nucleophilic groups borne by the proteins.

Only applicant has shown that this problem could be solved by the use of a 17α-alkyl carbonate in place of the 17α-acyl, in a 17β-ester steroidal basic nucleus. Likely this is so because of the lower electrophilicity of the carbon in the carbonate, as opposed to the carbonyl carbon in the ester. A resonance interpretation makes this apparent.

And comparing the immediately aforesaid versus the carbonate and ester prior art, it is submitted that the claimed subject matter is manifestly patentable thereover.

Consider first that the file history of the '575 Stache et al patent itself demonstrates that the corticoid carbonates and esters are not equivalent. A copy of this Serial No. 216,258 file history is also attached; note especially the Stache et al Responses, and the Alpermann Declaration evidencing that indeed the carbonates and esters are not equivalent per In re Grunwell and Petrow, supra.

It too will be appreciated that the Stache et al carbonates actually teach away from applicant's specific 17α-carbonate-17β-carboxylates. The Stache et al compounds, as aforesaid, necessarily comprise a halogenated methyl

group, or a methylene bridge at the 21-position. In fact, in the file history of the '334 patent (Serial No. 930,194, copy also attached), it is explicitly recognized that 17-carbonate-21-hydroxy compounds (more akin to those of applicant) are unstable. Applicant's specific carbonates, however, are not only stable, but are even more stable than the carboxylates. This flies in the face of the Stache teachings. Further, the inactive metabolites of applicant's claimed compounds are themselves more stable then the metabolites of the carboxylates. Also consider that the Stache et al metabolites are active (or do not form metabolites and, hence, remain active), rather than inactive. Inactive metabolites, to reiterate, are the very prerequisites of a soft drug, a concept conspicuously alien to the prior art.

The Examiner also should not lose sight of the fact that prior art essentially the same as that already of record herein, namely, Phillipps et al, Edwards and Sarett et al, was judged and found infirm vis-a-vis the carbonates, whether singly or in any possible combination thereof, during the prosecution of the Stache et al applications. See again the attached file histories.

Next further addressing the prior art of record and the outstanding Official Action, and while certainly not required as per In re Grunwell and Petrow, supra, comparative data exist demonstrating the patentable non-obviousness of the claimed compounds versus the compounds of Phillipps et al (1) and (2), in the effects on granulation tissue formation

and thymus weight caused by implantation of cotton pellets in rats.

Thus, attached is a Declaration by Dr. Kazuyuki Nakagawa. As will be seen from Table 1 of the Declaration, the representative compounds of the two "primary" references effect significant decrease in the thymus weight, even at a very low dose of 10 or 30 μg/pellet.

On the other hand, the claimed compounds which correspond to the reference compounds tested in the Declaration do not effect such significant decrease in thymus weight at the same dosage level. Note the third compound in TABLE IV on page 41 of the Specification and the first compound in TABLE V-b on page 43 of the Specification.

In view of this, the two primary references, Phillipps et al (1) and (2) do not teach the unexpectedly low levels of systemic side effects of the claimed compounds, and certainly do not render the claimed invention obvious.

We also categorically dispute that Sarett et al teaches the "conventionality" of modifying hydroxy substituent with oxycarbonyloxy substituents at the 17α-position of the steroid nucleus.

In the first place, it is not understood how only one reference can show the "conventionality" of the oxycarbonyloxy modification. Surely, it cannot be said that Sarett et al "teaches" such modification to be conventional.

Furthermore, Sarett et al is only concerned with a completely different class of compounds. The compounds disclosed in Sarett et al are saturated and unsaturated 17α-hydroxy-20-keto-pregnane-17-carbonates which are markedly

different from the claimed androstane derivatives, especially in the absence of a hydroxyl group at the 11-position and the presence of the group $-CO-CH_2-Y$ (Y=halo or H) at the 17β-position. Such pregnane derivatives, which are ketone derivatives, are wholly distinct from the claimed androstane derivatives which comprise an ester function (i.e., having a $-CO-O-R_1$ group at the 17β-position).

From the viewpoint of pharmaceutical activity, the compounds of Sarett et al are disclosed to have progestational activity and to be valuable as esterus regulating agents. See Col. 1, lines 24 to 27 of the '675 patent. Such pharmaceutical activity is not even remotely akin to the anti-inflammatory activity possessed by the compounds of Phillipps et al (1) and (2) and by the claimed compounds.

Therefore, one skilled in the art would not be motivated to modify the 17α-position of the compounds of Phillipps et al (1) and (2) with an oxycarbonyloxy moiety. One skilled in the art could not predict what would happen when the alkanoyloxy group of the anti-inflammatory compounds of Phillipps et al is modified by the oxycarbonyloxy group "suggested" by Sarett et al to be responsible for a completely different and irrelevant pharmaceutical activity.

Furthermore, Sarett et al does not at all teach that such oxycarbonyloxy modification will result in a marked improvement in anti-inflammatory activity and concomitant marked decrease in systemic side effects.

To clarify this, see Experiment 2 of Dr. Nakagawa's Declaration. From Table 2 of the Declaration, it will be

seen that replacement of the alkanoyloxy group of the compounds of Phillipps et al by the oxycarbonyloxy group results in marked increases in the therapeutic indices. The therapeutic index of the compound of Ex. 7A-3 is about 26 times higher than that of the corresponding compound of Phillipps et al, and the therapeutic index of the compound of Ex. 7A-12 is at least 10 times higher than that of the corresponding compound of Phillipps et al. This indicates that the oxycarbonyloxy replacement results in a significant increase in anti-inflammatory activity relative to lower systemic side effects. Such marked improvement is conspicuously absent from the teachings of Sarett et al and/or Phillipps et al (1) and (2).

In capsule summary, not even scintilla of evidence has been adduced supporting the proposition that applicant's particular steroidal mixed esters/carbonates would even be prima facie obvious. In re Grabiak, 226 U.S.P.Q. 870; In re Grunwell and Petrow, supra.

Lastly, for the sake of completeness, applicant herewith submits a copy of each reference made of record during the prosecution of his West German counterpart, namely:

(1) DE-OS 22 02 691

(2) DE-OS 23 36 633

(3) DE-OS 25 38 595

(4) DE-OS 29 04 6L4

(5) Anti-inflammatory Agents, Vol. 1, Academic Press, New York, San Francisco, London (1974), pages 275 and 270.

It appears that reference (2) corresponds to U. S. Patent No. 4,093,721 [Phillips (1)] and that reference (3) corresponds to U. S. Patent 3,856,828 [Phillipps (2)]. The translations of references (1), (4) and (5) are not available, but each cited reference relates only to 17α-acyloxy compounds, and they are at best cumulative.

Upon receipt hereof, if the Examiner remains at all unconvinced, he is requested to telephone the undersigned, at (703)836-6620, to schedule an interview.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is hereby earnestly solicited.

Respectfully submitted,

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